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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,481	JUNE ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-58 is/are pending in the application.

4a) Of the above claim(s) 36-40 and 53-58 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-35, 41-52 is/are rejected.

7)☒ Claim(s) 36-40 and 53-58 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 have been cancelled by Applicant's amendment filed on 04/20/2004. Claims 22-58 are still pending to which the following grounds of rejection are applicable.

Drawings

Fig. 9 is objected to because of an error in the label of "CD3" instead of αCD3 in panel B, p.7/13. Panel B indicates peak label of total RNA, IL-2 and HLA in the presence of optimal αCD3 antibody as described in p. 25, Example 3, second paragraph. Applicant is required to label the figure properly. The corrected drawing is required in reply of the Office action to avoid abandonment of the application. The requirement for corrected drawing will not be held in abeyance.

Claim Objections

Claims 38-40 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be phrased in the alternative.

The following is a quotation of MPEP § 608.01(n):

(c) One or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application. Any dependent claim which refers to more than one other claim ("multiple dependent claim ") shall refer to such other claims in the alternative only. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim.

Claims 38-40 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 36-40 have not been further treated on the merits.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 22 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about" is indefinite since the term does not appear to have been defined in the specification as to how many hours less than or more than 24 are included or excluded from the "about 24 hours". As an integer, the number 24 has to be clearly defined without ambiguity (e.g., 18 hours or 28 hours). The specification does not provide any indication as to what range of specific activity is covered by the term "about". See, Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Deletion of the term "about" in favor of replacement by the term "at most approximately 24 hours" would be most favorably considered to clarify indefiniteness.

Claims 28, 30, 33, 47, 50 rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. The term "fragment" is not defined in the specification. It is unclear to which fragment Applicant's limitation is referring.

Claim Rejections - 35 USC § 112 – written description

Claims 22-37 and 41-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 22-37 and 41-58, when given the broadest reasonable interpretation encompass a genus of unspecified stimulatory agents that increase the expression of an exogenous nucleic acid molecule in T-cells. The specification describes that contacting the T-cells *in vitro* with at least one stimulatory agent, e.g., a super-antigen, a combination of a phorbol ester and a calcium ionophore, or a protein kinase activator, wherein the T-cells are proliferating prior to contact with at least one stimulatory agent, forming stimulated proliferating T-cells, enhances transfection efficiency. The claim invention reads broadly on cells not proliferating before stimulation with a stimulatory agent. To the extend thaT-cells were not proliferating this rejection applies. Should the claims language be amended to recite the invention as cited in U. S. Patent No. 6,692,964, this rejection will be drop.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention.

Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that one skilled in the art could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant, provides a wide variety of agents that increase the expression of an exogenous nucleic acid molecules in T-cell (see, Fig. 8, for normalized CAT activity of prestimulated T-cells with anti-CD3 and anti-CD28 antibodies or Fig 15, for counts per minute from the nuclear fraction of T-cells stimulated with phorbol-12, 13-dibutyrate and ionomycin, 10 hours before transfection). However, even Applicant admits that some of the agents used to increase expression of exogenous nucleic acid molecule such as superantigens, which bridge the MHC II and TCR, may lead to cell activation, deletion or anergy (see, p. 30, lines 23-25). Further, the nature of the signal transduction pathways induced by superantigen

activation of T-cells remains a matter of controversy (see, p. 30, lines 33-34). Moreover, the specification does not provide any disclosure as to what would have been the required structure, which would cause any increase in the expression of an exogenous nucleic acid molecule in T-cells. Furthermore, such increased expression is not supported by consistency of results disclosed by Applicant, for example, activation with antibodies against the CD3 and CD28 receptors resulted in higher normalized CAT activity that activation with PDBU and IONO (see, Fig. 8), indicating that the signal-transducing evens of the intracellular pathways activated by these stimulatory agents reflect the complexity of the stimulatory signal supporting T-activation before transfection.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., expression of exogenous nucleic acid molecule in T-cells), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, there are not other disclosed characteristics in addition to the functional one discussed above. Such functional characteristic, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to

> complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any agent that increases expression of exogenous nucleic acid in T-cells, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claims 28, 30, 33, 47, 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention. The claim invention reads broadly on cells not proliferating before stimulation with a stimulatory agent. To the extend thaT-cells were not proliferating this rejection applies. Should the claims language be amended to recite the invention as cited in U. S. Patent No. 6,692,964, this rejection will be drop.

Claims 28, 30, 33, 47, 50 when given the broadest reasonable interpretation encompass a genus of unspecified fragments of a binding antigen, an anti-CD3 or anti-CD28 antibody. The specification specifically discloses the use of antibody G19-4 (anti-CD3) in Example 1, pp. 18-19, and of antibodies G19-4 (anti-CD3) and 9.3 (anti-CD28), in Example 2, p. 20, paragraph 3, for *in vitro* long-term culture of $CD28^+$ peripheral blood T lymphocytes. Additionally, Applicant discloses the use of superantigens as a stimulatory signal to induce T-cell proliferation prior to

transfection on p. 30, paragraph 3. However, Applicant has not described any other representative number of species by their complete structure to satisfy the written description requirements that could be used as a fragment of a binding antigen recognizing the T-cells expressing the TCR or a fragment of an anti-CD3 or anti-CD28 antibody to stimulate T-cells providing a primary activation signal and a second costimulatory signal. Moreover, the specification does not provide any disclosure as to what would have been the required structure of a" fragment thereof". Since no representative number of species have sufficiently been described by other relevant identifying characteristics (i.e., a combination of a first agent which provides a primary activation signal to the T-cell and a second agent which provides a costimulatory signal to introduce proliferation of T-cells), this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant a genus of unspecified fragments of a binding antigen, an anti-CD3 or anti-CD28 antibody, to introduce proliferation of activated T-cells, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-37 and 41-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 22-37 and 41-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for increasing the expression of an exogenous nucleic acid molecule comprising a gene, in T-cells, comprising:

contacting T-cells *in vitro* with at least one stimulatory agent, wherein the T-cells are proliferating prior to contact with the at least one stimulatory agent, forming stimulated proliferating T-cells; and

introducing an exogenous nucleic acid molecule comprising a gene into the proliferating, stimulated T-cells *in vitro*, at most approximately 24 hours after stimulation of said T-cells, such that the expression of the gene is increased in the T-cells.

does not reasonably provide enablement for a method for increasing the expression of an exogenous nucleic acid molecule in T-cells , comprising contacting the T-cell *in vitro* with any stimulatory agent. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. The claim invention embraces cells not proliferating before stimulation with a stimulatory agent. To the extend thaT-cells were not proliferating this rejection applies. Should the claims language be amended to recite the invention as cited in U. S. Patent No. 6,692,964, this rejection will be drop.

Claims 22-37 and 41-58 are drawn to a method for increasing the expression of an exogenous nucleic acid molecule comprising a gene, in T-cells, e.g. primary T-cells. The method includes contacting the T-cells *in vitro* with at least one stimulatory agent, e.g., a super-antigen, a

combination of a phorbol ester and a calcium ionophore, a protein kinase activator, or antibodies, wherein the T-cells are proliferating prior to contact with the at least one stimulatory agent, forming stimulated proliferating T-cells, and introducing an exogenous nucleic acid molecule comprising a gene into the proliferating, stimulated T-cells, *in vitro*, 24 hours of less after stimulation of the proliferating T-cells.

The specification specifically discloses the use of antibodies G19-4 (anti-CD3) and 9.3 (anti-CD28), phorbol-12,13-dibutyrate (phorbol ester), ionomycin or A23187 (calcium ionophore) and superantigens as stimulatory agents; however, the specification does not give any guidance as to other agents with can be used to stimulate and induce proliferation of T-cells by binding to T-cell surface molecules or by increasing intracellular calcium levels and activating protein kinase C. Other costimulatory molecules have been described (e.g., ICAM-1) that in combination with anti-CD3 antibody (i.e., OKT3) leads to activation of resting T-cell. Though the costimulatory pathways for T-cell activation have been describe, the mode of action has been poorly studied (see, Seventer Van et al., 1993, Journal of Immunology, p. 3879, col 1, paragraph 3). Moreover, antibodies directed against the same surface molecule may be stimulatory or inhibitory depending on the particular epitopes to which the antibody binds. Paul stays: "It is of interest that mAb reactive with the TCR differ in their ability to function as agonists" (Fundamental Immunology, Raven Press, NY 1989, p 364, col 1 lines 54-55) and " The ability of hese antibodies to function as either agonists or antagonists in a particular experimental model probably depends on the conditions under which they are used" (p.364, col 2, lines 3-6). This statement establishes the highly experimental and unpredictable nature of the field of antibody-mediated T-cell activation. Additionally, the specification does not disclose a source for the

antibodies used which would make them available to the public. It is highly improvable that other monoclonal antibodies generated against T-cell surface molecules would have the same binding epitope (e.g., affinity, avidity) as the antibodies used in the examples of the specification.

As such, and to the extent that the claimed invention is drawn to the make and use of a method for increasing the expression of an exogenous nucleic acid molecule in T-cells , comprising contacting the T-cell *in vitro* with any stimulatory agent, the as-filed application does not provide sufficient guidance and/or working examples for a skilled artisan to reasonably enable the claimed invention. In order to practice the claimed invention particularly in light of the unpredictability to make and use a method for increasing the expression of an exogenous nucleic acid molecule in T-cells, comprising contacting the T-cell *in vitro* with any stimulatory agent, one skilled in the Art would not find it reasonably predictable how said method would increase the expression of an exogenous nucleic acid molecule in T-cells. Due to the large quantity of experimentation necessary to generate the infinite number of derivative as recite in claims 22-35 and 41-52 and subsequent screening for expression of an exogenous DNA in primary T-cells using any stimulating agent, one skilled in the Art will have to perform extensive experimentation with each of these parameters to find the embodiments embraced by Applicant' claims, and as such, this experimentation would be considered undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22-27, 29, 31, 32, 36, 37, 41-46, 48, 49, and 55-58 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al. (US Patent No. 5,399,346).

Claims 22-27, 29, 31, 32, 36, 37, 41-46, 48, 49, and 55-58 are drawn to an *in vitro* method of transfecting T-cells comprising contacting primary T-cells with stimulatory and costimulatory agents that induce cells to activate and proliferate. Claims 29, 31, 32, 46, 48 and 49, further limit claims 22, 26, 41 or 45, to a stimulatory agent to the T-cell receptor/CD3 complex, CD2 molecule, an antigen-presenting cell (APC) and a natural ligand of CD28. Claims 23, 24, 25, 42, 43 and 44 further limit claims 22 and 41 to the use of a viral vector to introduce into the T-cell the exogenous nucleic acid molecule, specifically retrovirus vectors.

Anderson et al., discloses a method of transfecting T-cells comprising culturing primary T-cells in the presence of stimulatory and costimulatory agents. Specifically, Anderson et al., culture primary T-cells in the presence of the antigen sperm whale myoglobin (SWM) and APC (col. 6 lines 46-50). When T-cells are cultured under these conditions, the antigen is presented to the T-cells in such a way that the T-cell receptor is stimulated and T-cell proliferate (col. 7, lines 12-15). Anderson further discloses how exogenous genes are introduced into murine derived T-cells after 3 days of antigen stimulation and proliferation of T-cells (col. 10, lines1-7). Anderson et al., do not discuss the surface antigens of the T-cells and APC; however, it is known in the art

of immunology at the time of the invention that APC interacts with T-cells surface molecules CD2, CD3, CD28, Thy-1 and Ly-6 (Paul, W.E. Fundamental Immunology, Raven Press, NY 1989, pages 359-384, specifically fig. 1). Therefore the stimulation of these surface antigens on T-cells is an inherent property of T-cell stimulation by APC and occurs whenever an APC specifically stimulates a T-cell. Claim 27 introduces the limitation of a stimulatory agent comprising a protein tyrosine kinase activator. However, activation of the tyrosine kinase pathway is a well-known second messenger transmembrane signal. Indeed, activation of tyrosine kinase and phosphorilation of tyrosine in CD3ζ is recognized to occur as a result of the T-cell receptor activation by APC (see, Paul Table 3, page 378). Thus, tyrosine kinase activation is an inherent feature of T-cell receptor activation, since any antigen, which binds to the T-cell receptor, activates protein tyrosine kinase.

Additionally, Anderson teaches the insertion of a DNA molecule encoding a therapeutic protein into a human cell by a viral vector, specifically a retroviral vector (claim 9). Specifically, Anderson uses a moloney virus based vector with the neomycin resistant gene and the retroviral LTR to insert the genes for human adenosine deaminase into murine T-cells (column 6, lines 33-40). Moreover, Anderson's invention embraces other vectors besides retroviral vectors such as vector derived from DNA viruses and other RNA viruses (column 4, lines 42-49). Claims 24 and 44 introduce the limitation of a recombinant retrovirus that is replication defective. Anderson et al., do not discuss the use of replication defective vectors; however, it is known in the art of gene transfer and therapy at the time of the invention that elimination of retroviral genes is a critical step in vector systems used for gene transfer to reduce production of replication competent viruses (Verna et al., Nature, 1997, p. 240, paragraph 4). Further, the 1995 Report and

Recommendations of the Panel to Asses the NIH Investment in Research on Gene Therapy, Table 1, on pages 21-22 discloses exclusively the use retrovirus vectors with no viral genes.

Thus Anderson et al. in US Patent No. 5,399,346 anticipates and embraces the disclosed invention as set forth in the instant Application and teaches all the claimed limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-26, 28, 30, 33-35, 41, 45, 47, 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US Patent No. 5,399,346) in view of Nabel et al., WO 94/29436, international filing date June 3, 1994.

Claims 22-26, 28, 30, 33-35, 41, 45, 47, 50-54 are drawn to methods of transfecting T-cells which have been contacted and induced to proliferate *in vitro* by interaction with and α-CD3 antibodies or α-CD28 ligands.

Anderson et al., in '346 teaches a method of transfecting T-cell comprising culturing the T-cells in the presence of antigen and APC. As a result, these T-cells are stimulated and proliferate due to costimulation of the T-cell receptor (CD3) and CD28 receptor by their natural ligands. Anderson does not specifically teach the use of anti-CD3 antibodies to activate T-cells in place of an antigen presented by the APC or name the specific natural ligands of the CD28 receptor, B7-1 or B-72, to induce T-cell activation and proliferation.

Nabel et al., in WO 94/29436, filing date June 3, 1994, discusses activation and proliferation of a T-cell population by activating a T-cell receptor and stimulating an accessory molecule, wherein activation is accomplished by contacting the T-cells with a first agent that stimulates the TCR/CD3 complex and a second agent that stimulates an accessory molecule on the surface of the T-cell resulting in proliferation. Nabel et al., teaches that an anti-CD3 antibody, an anti CD2 antibody or a protein kinase C activator (PKC) in conjunction with a calcium ionophore is used as the first agent to activate T-cells (see, p. 1 lines 35-40; and p.2 lines 1-6). Co-stimulation of an accessory molecule on the surface of T-cell to induce proliferation is accomplished with an anti-CD28 antibody (i.e., ES5.2D8) or the CD28 ligands B7-1 or B7-2 (see, p. 2, lines 7-25).

Thus, it would have been obvious to one of ordinary skill in the art to induce activation and proliferation of the T-cell population described by Anderson et al., in '346 for subsequent transfection by contacting the cells with an antibody to the TCR/CD3 complex instead of

presenting the processed antigen in the surface of the APC against the TCR/CD3 complex. Additionally, Nabel et al., in WO 94/29436 discusses a primary activation signal of the TCR/CD3 complex-associated signal in a T-cell involving a combination of a PKC activator such as a phorbol ester (e.g., phorbol myristate acetate) and a calcium ionophore (e.g., ionomycin, which raises cytoplasmic calcium concentrations, see, p.5, lines 11-14). Hence, one of ordinary skill in the art can select different agents to contact primary T-cells *in vitro* to receive a primary signal either by direct activation of the TCR/CD3 complex or by bypassing the receptor and directly T-cell intracellular associated pathways, as taught by Nabel et al. Moreover, Nabel et al. discloses specific second costimulatory molecules necessary for T-cell proliferation after activation of the TCR/CD3 receptor (i.e., B7-1, B7-2, see p.2 lines 22-24). Hence, it would be obvious to one skilled in the art to stimulate T-cells before transfection as disclosed by Anderson with a combination of agents selected from α -CD3 and α-CD28 antibodies or CD28 ligands, or a combination of phorbol ester and a calcium ionophore. Thus the claimed invention was *prima facie* obvious at the time the invention was made.

Claim 27 rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US Patent No. 5,399,346) in view of Nabel et al., WO 94/29436 as applied to claims 22-26, 28, 30, 33-35, 41, 45, 47, 50-54 above, and further in view of Pullen (Superantigens. In Encyclopedia of Immunology, I.M. Roitt and P.J. Delves, eds. Academic Press, New York, 1993, pages 1406-1408).

Claim 27 is drawn to a method of transfecting T-cells by first stimulating them with a superantigen. Anderson in Patent in '346 teaches a method of transfecting T-cells comprising

culturing the T-cells in the presence of antigen and APC, but doesn't activation with superantigens. Pullen teaches (p. 1406 col 1, line 37 to p. 1407, col 1, line 14) that superantigens are known in the art as antigens which do not require processing by APC, to induce T-cell activation and proliferation. The only use disclosed in the instant application for superantigens is as a stimulatory signal to induce T-cell proliferation prior to transfection. Thus, it would have been obvious to a person skilled in the art to stimulate T-cells prior to transfection, as claimed by Anderson, using superantigens as taught by Pullen, to transfect the primary T-cells of the instantly claimed invention with a reasonable expectation of success. Thus the claimed invention was *prima facie* obvious at the time the invention was made.

Claim Rejections

Provisional *Rejection, Obviousness Type Double Patenting-No secondary Refence(s)*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-37 and 41-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-58 of U. S. of copending Application No. 10/658,787, filing date September 9, 2003. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 22-37 and 41-58 of the '787 application and claims 22, 26-35 and 41, 45-52 of this instant application are all encompass of an *in vitro* method for expressing an exogenous nucleic acid molecule in T-cells comprising:

(a) contacting T-cells *in vitro* with at least one stimulatory agent; and

(b) introducing an exogenous nucleic acid molecule into the T-cells less than about 24 hours after contacting said T-cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Rejection, Obviousness Type Double Patenting-No secondary Refence(s)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-37 and 41-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U. S. Patent No. 6,692,964, filing date June 7, 1995. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-15, 18 and 19 of the '964 patent and claims 22, 26-37, 41, 45-58 of this instant application are all encompass of an *in vitro* method for expressing an exogenous nucleic acid molecule in T-cells comprising:

(a) contacting T-cells *in vitro* with at least one stimulatory agent; and

(b) introducing an exogenous nucleic acid molecule into the T-cells less than about 24 hours after contacting said T-cells.

Because claims 22, 26-37, 41, 45-58 are drawn broadly to any method of transfecting T-cells *in vitro* after contacting them with at least one stimulatory agent, thus claims 22, 26-37, 41, 45-58 of the instant application embrace the invention as set forth and claimed in the '964 patent. Hence the method for *in vitro* T-cells transfection wherein T-cells are proliferating before contacting them with at least one stimulatory agent as claimed in the '964 patent and this instant application are obvious variants of one another.

Conclusion

Claims 22-37 and 41-58 are not allowed.

Information Disclosure Statement. No copy of References.

The information disclosure statement filed 10/28/2005, 12/02/2004 and 04/24/2004 fail to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the

application file, but the information referred to therein has not been considered. Moreover, these information was not found in the parent application No. 08/475,136, filed June 7, 1995. Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Those citations not considered by the examiner will have a line drawn through the citation and citations considered will have the examiner's initial adjacent thereto. A submission of a legible copy of each cited non-patent literature publication or that portion which caused it to be listed is required for examination.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F from 8:00 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nguyen Dave can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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